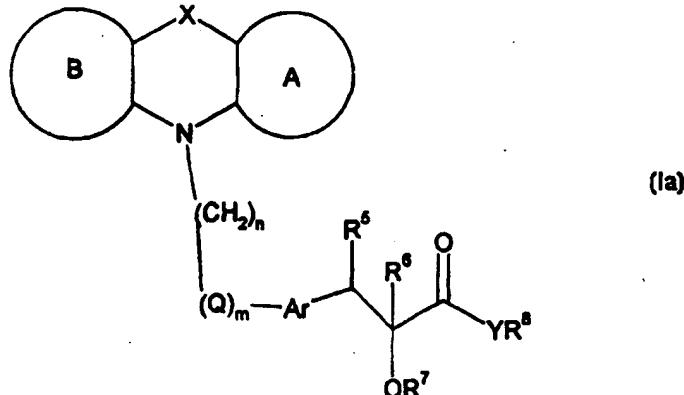




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 487/14, 471/14, 491/153, 495/14, A61K 31/4353, 31/407, A61P 3/04, 3/10		A1	(11) International Publication Number: WO 00/23451 (43) International Publication Date: 27 April 2000 (27.04.00)
(21) International Application Number: PCT/DK99/00573 (22) International Filing Date: 19 October 1999 (19.10.99)		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(30) Priority Data: PA 1998 01354 21 October 1998 (21.10.98) DK		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(71) Applicants: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK). DR. REDDY'S RESEARCH FOUNDATION [IN/IN]; 7-1-27, Ameerpet, 500 016 Hyderabad, A.P. (IN).			
(72) Inventors: JEPPESEN, Lone; Malmosevej 121, DK-2830 Virum (DK). BURY, Paul, Stanley; Hjortholms Allé 48, DK-2400 København NV (DK). SAUERBERG, Per, Syrenvænget 27, DK-3520 Farum (DK).			
(74) Common Representative: NOVO NORDISK A/S; Corporate Patents, Novo Allé, DK-2880 Bagsværd (DK).			

(54) Title: NEW COMPOUNDS, THEIR PREPARATION AND USE



(57) Abstract

The present invention relates to compounds of general formula (Ia). The compounds are useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslavia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

New Compounds, their Preparation and UseFIELD OF INVENTION

5 The present invention relates to novel compounds, pharmaceutical compositions containing them, methods for preparing the compounds and their use as medicaments. More specifically, compounds of the invention can be utilised in the treatment of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR). The present compounds reduce blood glucose and triglyceride levels and are accordingly

10 useful for the treatment of ailments and disorders such as diabetes and obesity.

The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, pharmaceutically acceptable solvates and pharmaceutical compositions containing them.

15 The compounds are useful for the treatment and/or prophylaxis of insulin resistance (type 2 diabetes), impaired glucose tolerance, dyslipidemia, disorders related to Syndrome X such as hypertension, obesity, insulin resistance, hyperglycaemia, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders. The compounds of the present invention are also useful for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis. These compounds may also be useful for improving cognitive functions in dementia, treating diabetic complications, psoriasis, polycystic ovarian syndrome (PCOS) and prevention and 20 treatment of bone loss, e.g. osteoporosis.

25

BACKGROUND OF THE INVENTION

30 Coronary artery disease (CAD) is the major cause of death in type 2 diabetic and metabolic syndrome patients (i.e. patients that fall within the 'deadly quartet' category of impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

The hypolipidaemic fibrates and antidiabetic thiazolidinediones separately display moderately effective triglyceride-lowering activities although they are neither potent nor efficacious enough to be a single therapy of choice for the dyslipidaemia often observed in type 2 diabetic or metabolic syndrome patients. The thiazolidinediones also potently lower circulating

5 glucose levels of type 2 diabetic animal models and humans. However, the fibrate class of compounds are without beneficial effects on glycaemia. Studies on the molecular actions of these compounds indicate that thiazolidinediones and fibrates exert their action by activating distinct transcription factors of the peroxisome proliferator activated receptor (PPAR) family, resulting in increased and decreased expression of specific enzymes and apolipoproteins
10 respectively, both key-players in regulation of plasma triglyceride content. Fibrates, on the one hand, are PPAR α activators, acting primarily in the liver. Thiazolidinediones, on the other hand, are high affinity ligands for PPAR γ acting primarily on adipose tissue.

Adipose tissue plays a central role in lipid homeostasis and the maintenance of energy

15 balance in vertebrates. Adipocytes store energy in the form of triglycerides during periods of nutritional affluence and release it in the form of free fatty acids at times of nutritional deprivation. The development of white adipose tissue is the result of a continuous differentiation process throughout life. Much evidence points to the central role of PPAR γ activation in initiating and regulating this cell differentiation. Several highly specialised
20 proteins are induced during adipocyte differentiation, most of them being involved in lipid storage and metabolism. The exact link from activation of PPAR γ to changes in glucose metabolism, most notably a decrease in insulin resistance in muscle, has not yet been clarified. A possible link is via free fatty acids such that activation of PPAR γ induces Lipoprotein Lipase (LPL), Fatty Acid Transport Protein (FATP) and Acyl-CoA Synthetase
25 (ACS) in adipose tissue but not in muscle tissue. This, in turn, reduces the concentration of free fatty acids in plasma dramatically, and due to substrate competition at the cellular level, skeletal muscle and other tissues with high metabolic rates eventually switch from fatty acid oxidation to glucose oxidation with decreased insulin resistance as a consequence.

30 PPAR α is involved in stimulating β -oxidation of fatty acids. In rodents, a PPAR α -mediated change in the expression of genes involved in fatty acid metabolism lies at the basis of the phenomenon of peroxisome proliferation, a pleiotropic cellular response, mainly limited to liver and kidney and which can lead to hepatocarcinogenesis in rodents. The phenomenon of peroxisome proliferation is not seen in man. In addition to its role in peroxisome

proliferation in rodents, PPAR α is also involved in the control of HDL cholesterol levels in rodents and humans. This effect is, at least partially, based on a PPAR α -mediated transcriptional regulation of the major HDL apolipoproteins, apo A-I and apo A-II. The hypotriglyceridemic action of fibrates and fatty acids also involves PPAR α and can be summarised as follows: (I) an increased lipolysis and clearance of remnant particles, due to changes in lipoprotein lipase and apo C-III levels, (II) a stimulation of cellular fatty acid uptake and their subsequent conversion to acyl-CoA derivatives by the induction of fatty acid binding protein and acyl-CoA synthase, (III) an induction of fatty acid b-oxidation pathways, (IV) a reduction in fatty acid and triglyceride synthesis, and finally (V) a decrease in VLDL production. Hence, both enhanced catabolism of triglyceride-rich particles as well as reduced secretion of VLDL particles constitutes mechanisms that contribute to the hypolipidemic effect of fibrates.

A number of compounds have been reported to be useful in the treatment of hyperglycemia, hyperlipidemia and hypercholesterolemia (U.S. Pat. 5,306,726, PCT Publications nos. WO91/19702, WO 95/03038, WO 96/04260, WO 94/13650, WO 94/01420, WO 97/36579, WO 97/25042, WO 95/17394, WO 99/08501, WO 99/19313 and WO 99/16758).

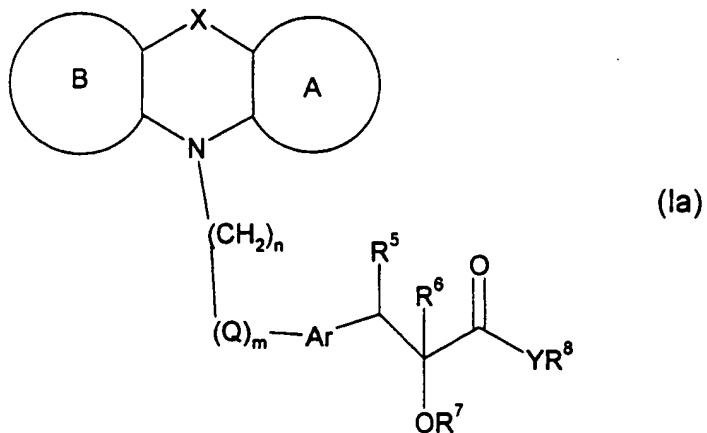
20 **SUMMARY OF THE INVENTION**

It seems more and more apparent that glucose lowering as a single approach does not overcome the macrovascular complications associated with type 2 diabetes and metabolic syndrome. Novel treatments of type 2 diabetes and metabolic syndrome must therefore aim at lowering both the overt hypertriglyceridaemia associated with these syndromes as well as alleviation of hyperglycaemia.

The clinical activity of fibrates and thiazolidinediones indicates that research for compounds displaying combined PPAR α and PPAR γ activation should lead to the discovery of efficacious glucose and triglyceride lowering drugs that have great potential in the treatment of type 2 diabetes and the metabolic syndrome (i.e. impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention relates to compounds of the general formula (Ia):



5

wherein ring A fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC₁₋₁₂alkyl, amino, acylamino, C₁₋₁₂alkyl-amino, arylamino, aralkylamino, aminoC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C₁₋₁₂alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₁₂alkyl, aralkoxyC₁₋₁₂alkyl, C₁₋₁₂alkylthio, thioC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆alkoxy or amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

ring B fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, acyl, acyloxy, hydroxyC₁₋₁₂alkyl, amino, acylamino, C₁₋₁₂alkyl-amino, arylamino, aralkylamino, aminoC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C₁₋₁₂alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₁₂alkyl, aralkoxyC₁₋₁₂alkyl, C₁₋₁₂alkylthio, thioC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆alkoxy or amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

C_{1-12} alkylthio, thio C_{1-12} alkyl, C_{1-12} alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, halogen, perhalomethyl, C_{1-6} alkoxy or amino optionally substituted with one or more C_{1-6} alkyl, perhalomethyl or aryl; optionally

5 substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂-, -CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -(NR⁹)-CH₂-, -(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-CH₂-, -(C=O)-, -O-CH₂-O-, -(NR⁹)-, -(NR⁹)-S(O₂)-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-(SO)-, -S-, -(SO)-, -(SO₂)-, -CH₂-

10 (SO₂)-, -CH₂-O-CH₂-, wherein R⁹ is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C_{1-12} alkyl, C_{1-12} alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclil, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C_{1-12} alkyl-amino, arylamino, aralkylamino, amino C_{1-12} alkyl, C_{1-12} alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C_{1-12} alkoxy C_{1-12} alkyl, aryloxy C_{1-12} alkyl, aralkoxy C_{1-12} alkyl, C_{1-12} alkylthio, thio C_{1-12} alkyl, C_{1-12} alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, halogen, C_{1-6} alkoxy, amino optionally substituted with one or more C_{1-6} alkyl, perhalomethyl or aryl;

15 Q is -O-, -S-, >SO₂, >NR¹³, wherein R¹³ is hydrogen or C_{1-6} alkyl,

20 Ar represents arylene, heteroarylene, or a divalent heterocyclic group optionally substituted with one or more C_{1-6} alkyl or aryl;

R⁵ represents hydrogen, hydroxy, halogen, C_{1-12} alkoxy, C_{1-12} alkyl, C_{4-12} -alkenynyl, C_{2-12} -alkenyl, C_{2-12} -alkynyl or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R⁵ forms a bond together with R⁶,

25 R⁶ represents hydrogen, hydroxy, halogen, C_{1-12} alkoxy, C_{1-12} alkyl, C_{4-12} -alkenynyl, C_{2-12} -alkenyl, C_{2-12} -alkynyl, acyl or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R⁶ forms a bond together with R⁵,

R⁷ represents hydrogen, C_{1-12} alkyl, C_{4-12} -alkenynyl, C_{2-12} -alkenyl, C_{2-12} -alkynyl, aryl, aralkyl, C_{1-12} alkoxy C_{1-12} alkyl, C_{1-12} alkoxycarbonyl, aryloxycarbonyl, C_{1-12} alkylaminocarbonyl, arylamino-

30 carbonyl, acyl, heterocyclil, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

R⁸ represents hydrogen, C_{1-12} alkyl, C_{4-12} -alkenynyl, C_{2-12} -alkenyl, C_{2-12} -alkynyl, aryl, aralkyl, heterocyclil, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

Y represents oxygen, sulphur or NR¹⁰, where R¹⁰ represents hydrogen, C₁₋₁₂alkyl, aryl, hydroxyC₁₋₁₂alkyl or aralkyl groups or when Y is NR¹⁰, R⁸ and R¹⁰ may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C₁₋₆alkyl; n is an integer ranging from 1 to 4 and m is an integer ranging from 0 to 1,

5 provided that A or B does not represent phenyl;
or a pharmaceutically acceptable salt thereof.

In a preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A fused to the ring containing X and N represents a 5-6

10 membered cyclic ring, optionally substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇alkenynyl, C₂₋₇alkenyl, C₂₋₇alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC₁₋₇alkyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl, C₁₋₇alkoxycarbonylamino, aryloxcarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, perhalomethyl or amino

15 optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy or cyano;

20 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇alkenynyl, C₂₋₇alkenyl, C₂₋₇alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl; optionally substituted with one or more halogen or hydroxy;

25 30 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy or C₁₋₇alkyl, C₂₋₇alkenyl, C₂₋₇alkynyl, C₁₋₇

,alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heteroaryloxy, heteroaralkoxy, acyl, acylamino, aryloxyC₁₋₇alkyl.

In another preferred embodiment, the present invention is concerned with

- 5 compounds of formula I wherein ring A fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy or C₁₋₇alkyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy or aryl.
- 10 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen or halogen.
- 15 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring B fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC₁₋₇alkyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl, C₁₋₇alkoxycarbonylamino, aryloxcarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, perhalomethyl or amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy or cyano.

In another preferred embodiment, the present invention is concerned with

- 30 compounds of formula I wherein ring B fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, amino, acylamino, C₁₋₇alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy or cyano.

,alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl; optionally substituted with one or more halogen or hydroxy.

5 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring B fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy or C₁₋₇alkyl, C₂₋₇alkenyl, C₂₋₇alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heteroaryloxy, heteroaralkoxy, acyl, arylamino, aryloxyC₁₋₇alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring B fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy or C₁₋₇alkyl, C₂₋₇alkenyl, C₂₋₇alkynyl, C₁₋₇alkoxy or aryl.

15 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring B fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen or halogen.

20 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂- , -CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -(NR⁹)-CH₂- , -(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂- , -CH₂- , -(C=O)-, -O-CH₂-O-, -(NR⁹)-, -(NR⁹)-S(O₂)-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂- (SO)-, -S-, -(SO)-, -(SO₂)-, -CH₂-(SO₂)-, -CH₂-O-CH₂- , wherein R⁹ is hydrogen, halogen, hydroxy, cyano, C₁₋₇alkyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂-, -CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -(NR⁹)-CH₂-, -(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-CH₂- , -(C=O)-, -O-CH₂-O-, -(NR⁹)-, -(NR⁹)-S(O₂)-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-SO-, -S-, -(SO)-, -(SO₂)-, -CH₂-(SO₂)-, -CH₂-O-CH₂-, wherein R⁹ is hydrogen, halogen, hydroxy, C₁₋₇alkyl, C₁₋₇alkoxy, aryl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂-, -CH=CH-, -O-(CHR⁹)-, -S-(CHR⁹)-, -(NR⁹)-CH₂-, -(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-CH₂- , -(C=O)-, -O-CH₂-O-, -(NR⁹)-S(O₂)-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-(SO)-, -(SO)-, -(SO₂)-, -CH₂-(SO₂)-, -CH₂-O-CH₂-, wherein R⁹ is hydrogen, halogen, hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂-, -CH=CH-, -O-(CHR⁹)-, -(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-CH₂- , -(C=O)-, -O-CH₂-O-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-(SO)-, -(SO)-, -(SO₂)-, -CH₂-(SO₂)-, -CH₂-O-CH₂-, wherein R⁹ is hydrogen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is -O- or -S-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is -O-.

25 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents arylene, heteroarylene, or a divalent heterocyclic group optionally substituted with one or more C₁₋₆alkyl or aryl; R⁵ represents hydrogen, hydroxy, halogen, C₁₋₇alkoxy, C₁₋₇alkyl, C₄₋₇alkenynyl, C₂₋₇alkenyl, C₂₋₇; or R⁵ forms a bond together with R⁶.

30 R⁶ represents hydrogen, hydroxy, halogen, C₁₋₇alkoxy, C₁₋₇alkyl, C₄₋₇alkenynyl, C₂₋₇alkenyl, C₂₋₇alkynyl; or R⁶ forms a bond together with R⁵,

R⁷ represents hydrogen, C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, aryl, aralkyl, C₁₋₇alkoxyC₁₋₇alkyl, C₁₋₇alkoxycarbonyl, aryloxycarbonyl, C₁₋₇alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocycl, heteroaryl or heteroaralkyl groups;

R⁸ represents hydrogen, C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, aryl, aralkyl, heterocycl, heteroaryl or heteroaralkyl;

5 Y represents oxygen, sulphur or NR¹⁰, where R¹⁰ represents hydrogen, C₁₋₇alkyl, hydroxyC₁₋₇alkyl;

n is an integer ranging from 2 to 3 and m is an integer ranging from 0 to 1.

10 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents arylene or heteroarylene;

R⁵ represents hydrogen, hydroxy, halogen; or R⁵ forms a bond together with R⁶,

R⁶ represents hydrogen, hydroxy, halogen; or R⁶ forms a bond together with R⁵,

R⁷ represents hydrogen, C₁₋₇alkyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, aryl, aralkyl, C₁₋₇alkoxyC₁₋₇alkyl,

15 C₁₋₇alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocycl, heteroaryl or heteroaralkyl groups;

R⁸ represents hydrogen, C₁₋₇alkyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl,;

Y represents oxygen or sulphur;

n is an integer ranging from 2 to 3 and m is 1.

20 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents arylene or heteroarylene;

R⁵ represents hydrogen.

R⁶ represents hydrogen;

25 R⁷ represents hydrogen, C₁₋₇alkyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, aryl, aralkyl, C₁₋₇alkoxyC₁₋₇alkyl;

R⁸ represents hydrogen, C₁₋₇alkyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl,;

Y represents oxygen;

n is an integer ranging from 2 to 3 and m is 1.

30 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents arylene;

R⁵ represents hydrogen;

R⁶ represents hydrogen;

R⁷ represents hydrogen, C₁₋₄alkyl, C₂₋₄-alkenyl, C₂₋₄-alkynyl,

R^8 represents hydrogen, C_{1-4} alkyl,
Y represents oxygen;
n is an integer ranging from 2 to 3 and m is 1.

5 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents phenylene;

R^5 represents hydrogen;

R^6 represents hydrogen;

R^7 represents hydrogen, C_{1-4} alkyl,

10 R^8 represents hydrogen

Y represents oxygen;

n is an integer ranging from 2 to 3 and m is 1.

15 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein A is 5 membered cyclic ring containing S.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein B is 5 membered cyclic ring containing S.

20 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is $-CH=(CR^9)-$, wherein R^9 is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein n is 2.

25

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is $-O-$.

30 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein m is 1.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar is phenylene.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁵ is H.

5 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁶ is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁷ is ethyl.

10 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Y is oxygen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁸ is H.

15

Preferred compounds of the invention are:

3-[4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[f]azulen-4-yl)-ethoxy]-phenyl]-2-ethoxy-
propionic acid,

20 3-[4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[f]azulen-4-yl)-ethoxy]-phenyl]-2-methoxy-
propionic acid,

3-[4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[f]azulen-4-yl)-ethoxy]-phenyl]-2-propoxy-
propionic acid,

3-[4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[f]azulen-4-yl)-ethoxy]-phenyl]-2-benzyloxy-
propionic acid,

25 3-[4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[f]azulen-4-yl)-ethyl]-phenyl]-2-ethoxy-
propionic acid,

3-[4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[f]azulen-4-yl)-ethyl]-phenyl]-2-methoxy-
propionic acid,

30 3-[4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[f]azulen-4-yl)-ethyl]-phenyl]-2-propoxy-
propionic acid,

3-[4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[f]azulen-4-yl)-ethyl]-phenyl]-2-benzyloxy-
propionic acid,

3-[4-[1-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[f]azulen-4-yl)-methoxy]-phenyl]-2-ethoxy-
propionic acid,

3-{4-[1-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-methoxy]-phenyl}-2-methoxy-propionic acid,

3-{4-[1-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-methoxy]-phenyl}-2-benzyloxy-propionic acid,

5 3-{4-[3-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-propoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[3-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-propoxy]-phenyl}-2-methoxy-propionic acid,

3-{4-[3-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-propoxy]-phenyl}-2-

10 benzyloxy-propionic acid,

3-{4-[3-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-propyl]-phenyl}-2-ethoxy-propionic acid,

3-{4-[3-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-propyl]-phenyl}-2-methoxy-propionic acid,

15 3-{4-[3-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-propyl]-phenyl}-2-benzyloxy-propionic acid,

2-Ethoxy-3-(4-(2-(9*H*-1,8,10-triaza-anthracen-10-yl)-ethoxy)-phenyl)-propionic acid,

2-methoxy-3-(4-(2-(9*H*-1,8,10-triaza-anthracen-10-yl)-ethoxy)-phenyl)-propionic acid,

2-propoxy-3-(4-(2-(9*H*-1,8,10-triaza-anthracen-10-yl)-ethoxy)-phenyl)-propionic acid,

20 2-benzyloxy-3-(4-(2-(9*H*-1,8,10-triaza-anthracen-10-yl)-ethoxy)-phenyl)-propionic acid,

2-ethoxy-3-(4-(1-(9*H*-1,8,10-triaza-anthracen-10-yl)-methoxy)-phenyl)-propionic acid,

2-methoxy-3-(4-(1-(9*H*-1,8,10-triaza-anthracen-10-yl)-methoxy)-phenyl)-propionic acid,

2-benzyloxy-3-(4-(1-(9*H*-1,8,10-triaza-anthracen-10-yl)-methoxy)-phenyl)-propionic acid,

2-ethoxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propoxy)-phenyl)-propionic acid,

25 2-propoxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propoxy)-phenyl)-propionic acid,

2-methoxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propoxy)-phenyl)-propionic acid,

2-benzyloxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propoxy)-phenyl)-propionic acid,

2-ethoxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propyl)-phenyl)-propionic acid,

2-propoxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propyl)-phenyl)-propionic acid,

30 2-methoxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propyl)-phenyl)-propionic acid,

2-benzyloxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propyl)-phenyl)-propionic acid,

2-ethoxy-3-(4-(2-(4,5,9-triaza-fluoren-9-yl)-ethoxy)-phenyl)-propionic acid,

2-methoxy-3-(4-(2-(4,5,9-triaza-fluoren-9-yl)-ethoxy)-phenyl)-propionic acid,

2-propoxy-3-(4-(2-(4,5,9-triaza-fluoren-9-yl)-ethoxy)-phenyl)-propionic acid,

2-ethoxy-3-(4-(1-(4,5,9-triaza-fluoren-9-yl)-methoxy)-phenyl)-propionic acid,
2-methoxy-3-(4-(1-(4,5,9-triaza-fluoren-9-yl)-methoxy)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(1-(4,5,9-triaza-fluoren-9-yl)-methoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
5 2-methoxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
2-propoxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
2-methoxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
10 2-benzyloxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
2-propoxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
2-ethoxy-3-(4-(2-(1,8,9-triaza-fluoren-9-yl)-ethoxy)-phenyl)-propionic acid,
2-methoxy-3-(4-(2-(1,8,9-triaza-fluoren-9-yl)-ethoxy)-phenyl)-propionic acid,
2-propoxy-3-(4-(2-(1,8,9-triaza-fluoren-9-yl)-ethoxy)-phenyl)-propionic acid,
15 2-benzyloxy-3-(4-(2-(1,8,9-triaza-fluoren-9-yl)-ethoxy)-phenyl)-propionic acid,
2-methoxy-3-(4-(1-(1,8,9-triaza-fluoren-9-yl)-methoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(1-(1,8,9-triaza-fluoren-9-yl)-methoxy)-phenyl)-propionic acid,
2-propoxy-3-(4-(1-(1,8,9-triaza-fluoren-9-yl)-methoxy)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(1-(1,8,9-triaza-fluoren-9-yl)-methoxy)-phenyl)-propionic acid,
20 2-ethoxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
2-methoxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
2-propoxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
25 2-methoxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
2-propoxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
3-(4-(2-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-ethoxy-propionic acid,
3-(4-(2-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-methoxy-propionic acid,
30 3-(4-(2-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-propoxy-propionic acid,
3-(4-(2-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(1-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-methoxy-propionic acid,
3-(4-(1-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-ethoxy-propionic acid,
3-(4-(1-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-propoxy-propionic acid,

3-(4-(1-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-ethoxy-propionic acid,
3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-methoxy-propionic acid,
3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-propoxy-propionic acid,
5 3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-ethoxy-propionic acid,
3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-methoxy-propionic acid,
3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-propoxy-propionic acid,
3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-benzyloxy-propionic acid,
10 3-(4-(2-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-ethoxy-propionic acid,
3-(4-(2-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-methoxy-propionic acid,
3-(4-(2-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-propoxy-propionic acid,
3-(4-(2-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(1-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-ethoxy-propionic acid;
15 3-(4-(1-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-methoxy-propionic acid,
3-(4-(1-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-propoxy-propionic acid,
3-(4-(1-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-ethoxy-propionic acid,
3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-propoxy-propionic acid,
20 3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-methoxy-propionic acid,
3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-ethoxy-propionic acid,
3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-propoxy-propionic acid,
3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-methoxy-propionic acid,
25 3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(2-(4*H*-1,7-dithia-8-aza-*s*-indacen-8-yl)-ethoxy)-phenyl)-2-ethoxy-propionic acid,
3-(4-(2-(4*H*-1,7-dithia-8-aza-*s*-indacen-8-yl)-ethoxy)-phenyl)-2-methoxy-propionic acid,
3-(4-(2-(4*H*-1,7-dithia-8-aza-*s*-indacen-8-yl)-ethoxy)-phenyl)-2-propoxy-propionic acid,
3-(4-(2-(4*H*-1,7-dithia-8-aza-*s*-indacen-8-yl)-ethoxy)-phenyl)-2-benzyloxy-propionic acid,
30 3-(4-(1-(4*H*-1,7-dithia-8-aza-*s*-indacen-8-yl)-methoxy)-phenyl)-2-ethoxy-propionic acid,
3-(4-(1-(4*H*-1,7-dithia-8-aza-*s*-indacen-8-yl)-methoxy)-phenyl)-2-methoxy-propionic acid,
3-(4-(1-(4*H*-1,7-dithia-8-aza-*s*-indacen-8-yl)-methoxy)-phenyl)-2-propoxy-propionic acid,
3-(4-(1-(4*H*-1,7-dithia-8-aza-*s*-indacen-8-yl)-methoxy)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(3-(4*H*-1,7-dithia-8-aza-*s*-indacen-8-yl)-propoxy)-phenyl)-2-ethoxy-propionic acid,

3-(4-(3-(4H-1,7-dithia-8-aza-s-indacen-8-yl)-propoxy)-phenyl)-2-methoxy-propionic acid,
3-(4-(3-(4H-1,7-dithia-8-aza-s-indacen-8-yl)-propoxy)-phenyl)-2-propoxy-propionic acid,
3-(4-(3-(4H-1,7-dithia-8-aza-s-indacen-8-yl)-propoxy)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(3-(4H-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-2-ethoxy-propionic acid,
5 3-(4-(3-(4H-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-2-methoxy-propionic acid,
3-(4-(3-(4H-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-2-propoxy-propionic acid,
3-(4-(3-(4H-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-2-benzyloxy-propionic acid,
2-ethoxy-3-(4-(2-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-ethoxy)-phenyl)-propionic acid,
2-methoxy-3-(4-(2-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-ethoxy)-phenyl)-propionic acid,
10 2-propoxy-3-(4-(2-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-ethoxy)-phenyl)-propionic acid,
2-propoxy-3-(4-(2-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-ethoxy)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(2-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-ethoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(1-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-methoxy)-phenyl)-propionic acid,
2-methoxy-3-(4-(1-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-methoxy)-phenyl)-propionic acid,
15 2-propoxy-3-(4-(1-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-methoxy)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(1-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-methoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propoxy)-phenyl)-propionic acid,
2-methoxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propoxy)-phenyl)-propionic acid,
2-propoxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propoxy)-phenyl)-propionic acid,
20 2-benzyloxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-propionic acid,
2-methoxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-propionic acid,
2-propoxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-propionic acid;
25 or a pharmaceutically acceptable salt thereof.

A further preferred compound of the invention is:

3-[4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*J*]azulen-4-yl)-ethoxy]-phenyl]-2-ethoxy-
propionic acid;

30 or a pharmaceutically acceptable salt thereof.

In the above structural formulas and throughout the present specification, the following terms
have the indicated meaning:

The terms "C₁₋₁₂-alkyl" as used herein, alone or in combination is intended to include those alkyl groups of the designated length in either a linear or branched or cyclic configuration. represents e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like. Typical C₁₋₆-alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-
5 propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-pentyl, hexyl, iso-hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like.

The terms "C_{2-n}-alkenyl" wherein n' can be from 3 through 15, as used herein, represents an olefinically unsaturated branched or straight group having from 2 to the specified number of
10 carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, allyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, hexenyl, pentenyl, and the like.

The terms "C_{2-n}-alkynyl" wherein n' can be from 3 through 15, as used herein, represent an unsaturated branched or straight group having from 2 to the specified number of carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl and the like.
15

The terms "C_{4-n}-alkenynyl" wherein n' can be from 5 through 15, as used herein, represent an unsaturated branched or straight hydrocarbon group having from 4 to the specified number of carbon atoms and both at least one double bond and at least one triple bond. Examples of such groups include, but are not limited to, 1-penten-4-yne, 3-penten-1-yne, 1,3-hexadiene-5-yne and the like.
20

25 The term "C₁₋₁₂-alkoxy" as used herein, alone or in combination is intended to include those C₁₋₁₂-alkyl groups of the designated length in either a linear or branched or cyclic configuration linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy and isohexoxy. Examples of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.
30

The term "C₁₋₆-alkoxycarbonyloxy" is intended to include the above defined C₁₋₆-alkoxy groups attached to a carbonyloxy moiety, e.g. methoxycarbonyloxy, ethoxycarbonyloxy, etc..

As used herein the term "C₄₋₁₂-(cycloalkylalkyl)" represents a branched or straight alkyl group substituted at a carbon with a cycloalkyl group. Examples of such groups include, but are not limited to, cyclopropylethyl, cyclobutylmethyl, 2-(cyclohexyl)ethyl, cyclohexylmethyl, 3-(cyclopentyl)-1-propyl, and the like.

5

The term "C₁₋₁₂-alkylthio" as used herein, alone or in combination, refers to a straight or branched or cyclic monovalent substituent comprising a C₁₋₁₂-alkyl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom and having 1 to 12 carbon atoms e.g. methylthio, ethylthio, propylthio, butylthio, pentylthio. Example of cyclic alkylthio are cyclopropylthio, cyclobutylthio, cyclopentylthio and cyclohexylthio.

10

The term "C₁₋₁₂alkylamino" as used herein, alone or in combination, refers to a straight or branched or cyclic monovalent substituent comprising a C₁₋₁₂-alkyl group linked through amino having a free valence bond from the nitrogen atom e.g. methylamino, ethylamino, propylamino, butylamino, pentylamino. Example of cyclic alkylamino are cyclopropylamino, cyclobutylamino, cyclopentylamino and cyclohexylamino.

15

The term "hydroxyC₁₋₁₂alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂alkyl as defined herein whereto is attached a hydroxy group, e.g. hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl etc..

20

The term "arylamino" as used herein, alone or in combination, refers to an aryl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. phenylamino, naphthylamino, etc..

25

The term "aralkylamino" as used herein, alone or in combination, refers to an aralkyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. benzylamino, phenethylamino, 3-phenylpropylamino, 1-naphtylmethylamino, 2-(1-naphtyl)ethylamino and the like.

30

The term "aminoC₁₋₁₂alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂alkyl as defined herein whereto is attached an amino group, e.g. aminoethyl, 1-aminopropyl, 2-aminopropyl etc..

The term "aryloxycarbonyl" as used herein, alone or in combination, refers to an aryloxy as defined herein linked through a carbonyl having a free valence bond from the carbon atom, e.g. phenoxy carbonyl, 1-naphthyl oxycarbonyl or 2-naphthyl oxycarbonyl, etc..

- 5 The term "aralkoxycarbonyl" as used herein, alone or in combination, refers to an aralkoxy as defined herein linked through a carbonyl having a free valence bond from the carbon atom, e.g. benzyloxycarbonyl, phenethoxycarbonyl, 3-phenylpropoxycarbonyl, 1-naphthylmethoxycarbonyl, 2-(1-naphthyl)ethoxycarbonyl, etc..
- 10 The term "C₁₋₁₂alkoxyC₁₋₁₂alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂alkyl as defined herein whereto is attached a C₁₋₁₂alkoxy as defined herein, e.g. methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, etc..
- 15 The term "aryloxyC₁₋₁₂alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂alkyl as defined herein whereto is attached an aryloxy as defined herein, e.g. phenoxy methyl, phenoxydodecyl, 1-naphthyl oxyethyl, 2-naphthyl oxypropyl, etc..
- 20 The term "aralkoxyC₁₋₁₂alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂alkyl as defined herein whereto is attached an aralkoxy as defined herein, e.g. benzyloxymethyl, phenethoxydodecyl, 3-phenylpropoxyethyl, 1-naphthylmethoxypropyl, 2-(1-naphthyl)ethoxymethyl, etc..
- 25 The term "thioC₁₋₁₂alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂alkyl as defined herein whereto is attached a group of formula -SR''' wherein R''' is hydrogen, C₁₋₆alkyl or aryl, e.g. thiomethyl, methylthiomethyl, phenylthioethyl, etc..
- 30 The term "C₁₋₁₂alkoxycarbonylamino" as used herein, alone or in combination, refers to a C₁₋₁₂alkoxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. methoxycarbonylamino, carbethoxymino, propoxycarbonylamino, isopropoxycarbonylamino, n-butoxycarbonylamino, tert-butoxycarbonylamino, etc..
- 35 The term "aryloxycarbonylamino" as used herein, alone or in combination, refers to an aryloxycarbonyl as defined herein linked through amino having a free valence bond from the

nitrogen atom e.g. phenoxy carbonylamino, 1-naphthyl oxycarbonylamino or 2-naphthyl oxycarbonylamino, etc..

The term "aralkoxycarbonylamino" as used herein, alone or in combination, refers to an

5 aralkoxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. benzyloxycarbonylamino, phenethoxycarbonylamino, 3-phenylpropoxycarbonylamino, 1-naphthylmethoxycarbonylamino, 2-(1-naphthyl)ethoxycarbonylamino, etc..

10 The term "aryl" is intended to include aromatic rings, such as carboxylic aromatic rings selected from the group consisting of phenyl, naphthyl, (1-naphthyl or 2-naphthyl) optionally substituted with halogen, amino, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy.

The term "arylene" is intended to include divalent aromatic rings, such as carboxylic aromatic

15 rings selected from the group consisting of phenylene, naphthylene, optionally substituted with halogen, amino, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy.

The term "halogen" means fluorine, chlorine, bromine or iodine.

20 The term "perhalomethyl" means trifluoromethyl, trichloromethyl, tribromomethyl or triiodomethyl.

The term "C₁₋₆-dialkylamino" as used herein refers to an amino group wherein the two

hydrogen atoms independently are substituted with a straight or branched, saturated

25 hydrocarbon chain having the indicated number of carbon atoms; such as dimethylamino, N-ethyl-N-methylamino, diethylamino, dipropylamino, N-(n-butyl)-N-methylamino, di(n-pentyl)amino, and the like.

The term "acyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-alkyl

30 group linked through a carbonyl group; such as e.g. acetyl, propionyl, butyryl, isobutyryl, pivaloyl, valeryl, and the like.

The term "acyloxy" as used herein refers to acyl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom e.g. acetoxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy, valeryloxy, and the like.

5

The term "C₁₋₁₂-alkoxycarbonyl" as used herein refers to a monovalent substituent comprising a C₁₋₁₂-alkoxy group linked through a carbonyl group; such as e.g. methoxycarbonyl, carbethoxy, propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 3-methylbutoxycarbonyl, n-hexoxycarbonyl and the like.

10

The term "a cyclic ring containing from 5 to 7 carbon atoms" as used herein refers to a monocyclic saturated or unsaturated or aromatic system, wherein the ring may be cyclopentyl, cyclopentenyl, cyclohexyl, phenyl or cycloheptyl.

15

The term "bicycloalkyl" as used herein refers to a monovalent substituent comprising a bicyclic structure made of 6-12 carbon atoms such as e.g. 2-norbornyl, 7-norbornyl, 2-bicyclo[2.2.2]octyl and 9-bicyclo[3.3.1]nonanyl.

20

The term "heteroaryl" as used herein, alone or in combination, refers to a monovalent substituent comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. furan, thiophene, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine.

25

The term "heteroarylene" as used herein, alone or in combination, refers to a divalent group comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. furan, thiophene, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine.

The term "heteroaryloxy" as used herein, alone or in combination, refers to a heteroaryl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom e.g. pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, 5 quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine linked to oxygen.

The term "aralkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with an aromatic carbohydride; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphthylmethyl, 2-(1-naphthyl)ethyl and the like.

10 The term "aryloxy" as used herein refers to phenoxy, 1-naphthoxy or 2-naphthoxy.

The term "aralkoxy" as used herein refers to a C₁₋₆-alkoxy group substituted with an aromatic carbohydride, such as benzyloxy, phenethoxy, 3-phenylpropoxy, 1-naphthylmethoxy, 2-(1-15 naphthyl)ethoxy and the like.

The term "heteroaralkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with a heteroaryl group; such as (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-20 1-(2-pyrimidyl)ethyl and the like.

The term "heteroaralkoxy" as used herein refers to a heteroaralkyl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom, e.g. (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl linked to oxygen.

The term "C₁₋₆-alkylsulfonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-alkyl group linked through a sulfonyl group such as e.g. methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, sec-butylsulfonyl, isobutylsulfonyl, tert-30 butylsulfonyl, n-pentylsulfonyl, 2-methylbutylsulfonyl, 3-methylbutylsulfonyl, n-hexylsulfonyl, 4-methylpentylsulfonyl, neopentylsulfonyl, n-hexylsulfonyl and 2,2-dimethylpropylsulfonyl.

The term "C₁₋₆-monoalkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-monoalkylamino group linked through a sulfonyl group such as e.g.

m thylaminosulfonyl, ethylaminosulfonyl, n-propylaminosulfonyl, isopropylaminosulfonyl, n-butylaminosulfonyl, sec-butylaminosulfonyl, isobutylaminosulfonyl, tert-butylaminosulfonyl, n-pentylaminosulfonyl, 2-methylbutylaminosulfonyl, 3-methylbutylaminosulfonyl, n-hexylaminosulfonyl, 4-methylpentylaminosulfonyl, neopentylaminosulfonyl, n-hexylaminosulfonyl and 2,2-dimethylpropylaminosulfonyl.

The term "C₁₋₆-dialkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-dialkylamino group linked through a sulfonyl group such as dimethylaminosulfonyl, N-ethyl-N-methylaminosulfonyl, diethylaminosulfonyl, 10 dipropylaminosulfonyl, N-(n-butyl)-N-methylaminosulfonyl, di(n-pentyl)aminosulfonyl, and the like.

The term "C₁₋₆-alkylsulfinyl" as used herein refers to a monovalent substituent comprising a straight or branched C₁₋₆-alkyl group linked through a sulfinyl group (-S(=O)-); such as e.g. 15 methylsulfinyl, ethylsulfinyl, isopropylsulfinyl, butylsulfinyl, pentylsulfinyl, and the like.

The term "acylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with an acyl group, such as e.g. acetamido, propionamido, isopropylcarbonylamino, and the like.

20 The term "(C₃₋₆-cycloalkyl)C₁₋₆-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having 1 to 6 carbon atoms and being monosubstituted with a C₃₋₆-cycloalkyl group, the cycloalkyl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; such as e.g. cyclopropylmethyl, (1-25 methylcyclopropyl)methyl, 1-(cyclopropyl)ethyl, cyclopentylmethyl, cyclohexylmethyl, and the like.

The term "arylthio" as used herein, alone or in combination, refers to an aryl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom, the aryl group 30 optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; e.g. phenylthio, (4-methylphenyl)-thio, (2-chlorophenyl)thio, and the like.

The term "arylsulfinyl" as used herein refers to an aryl group linked through a sulfinyl group (-S(=O)-), the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; such as e.g. phenylsulfinyl, (4-chlorophenyl)sulfinyl, and the like.

5 The term "arylsulfonyl" as used herein refers to an aryl group linked through a sulfonyl group, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; such as e.g. phenylsulfonyl, tosyl, and the like.

The term "C₁₋₆-monoalkylaminocarbonyl" as used herein refers to a monovalent substituent
10 comprising a C₁₋₆-monoalkylamino group linked through a carbonyl group such as e.g. methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, n-butylaminocarbonyl, sec-butylaminocarbonyl, isobutylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, 2-methylbutylaminocarbonyl, 3-methylbutylaminocarbonyl, n-hexylaminocarbonyl, 4-methylpentylaminocarbonyl, neopentylaminocarbonyl, n-hexylaminocarbonyl and 2-2-dimethylpropylaminocarbonyl.

The term "C₁₋₆-dialkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-dialkylamino group linked through a carbonyl group such as dimethylaminocarbonyl, N-ethyl-N-methylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, N-(n-butyl)-N-methylaminocarbonyl, di(n-pentyl)aminocarbonyl, and the like.

The term "C₁₋₆-monoalkylaminocarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a C₁₋₆-monoalkylaminocarbonyl group, e.g. methylaminocarbonylamino, ethylamino-carbonylamino, n-propylaminocarbonylamino, 25 isopropylaminocarbonylamino, n-butylaminocarbonylamino, sec-butylaminocarbonylamino, isobutylaminocarbonylamino, tert-butylaminocarbonylamino, and 2-methylbutylaminocarbonylamino.

The term "C₁₋₆-dialkylaminocarbonylamino" as used herein refers to an amino group wherein 30 one of the hydrogen atoms is substituted with a C₁₋₆-dialkylaminocarbonyl group, such as dimethylaminocarbonylamino, N-ethyl-N-methylaminocarbonylamino, diethylaminocarbonylamino, dipropylaminocarbonylamino, N-(n-butyl)-N-methylaminocarbonylamino, di(n-pentyl)aminocarbonylamino, and the like.

As used herein, the phrase "heterocycll" means a monovalent saturated or unsaturated group being monocyclic and containing one or more, such as from one to four carbon atom(s), and from one to four N, O or S atom(s) or a combination thereof. The phrase "heterocycll" includes, but is not limited to, 5-membered heterocycles having one hetero

- 5 atom (e.g. pyrrolidine, pyrrolidine); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. pyrazoline, pyrazolidine, 1,2-oxathiolane, imidazolidine, imidazoline, 4-oxazolone); 5-membered heterocycles having three heteroatoms (e.g. tetrahydrofuran); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. piperidine); 6-membered heterocycles with two heteroatoms (e.g. piperazine, morpholine); 6-membered heterocycles with three heteroatoms; and 6-membered heterocycles with four heteroatoms.
- 10

As used herein, the phrase "a divalent heterocyclic group" means a divalent saturated or unsaturated system being monocyclic and containing one or more, such as from one to four

- 15 carbon atom(s), and one to four N, O or S atom(s) or a combination thereof. The phrase a divalent heterocyclic group includes, but is not limited to, 5-membered heterocycles having one hetero atom (e.g. pyrrolidine, pyrrolidine); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. pyrazoline, pyrazolidine, 1,2-oxathiolane, imidazolidine, imidazoline, 4-oxazolone); 5-membered heterocycles having three heteroatoms (e.g. tetrahy- drofuran); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. piperidine); 6-membered heterocycles with two heteroatoms (e.g. piperazine, morpholine); 6-membered heterocycles with three heteroatoms; and 6-membered heterocycles with four heteroatoms.
- 20

- 25 25 As used herein, the phrase "a 5-6 membered cyclic ring" means an unsaturated or saturated or aromatic system containing one or more carbon atoms and optionally from one to four N, O or S atom(s) or a combination thereof. The phrase "a 5-6 membered cyclic ring" includes, but is not limited to, e.g. cyclopentyl, cyclohexyl, phenyl, cyclohexenyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiomorpholinyl, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, 1,3-dioxolanyl, 1,4-dioxolanyl, 5-membered heterocycles having one hetero atom (e.g. thiophenes, pyrroles, furans); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. oxazoles, pyrazoles, imidazoles, thiazoles, purines); 5-membered heterocycles having thre
- 30

heteroatoms (e.g. triazoles, thiadiazoles); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. pyridine, quinoline, isoquinoline, phenanthridine, cyclohepta[b]pyridine); 6-membered heterocycles with two heteroatoms (e.g. pyridazines, cinnolines, phthalazines, pyrazines, pyrimidines, 5 quinazolines, morpholines); 6-membered heterocycles with three heteroatoms (e.g. 1,3,5-triazine); and 6-membered heterocycles with four heteroatoms.

As used herein, the phrase "5- or 6-membered nitrogen containing ring" refers to a monovalent substituent comprising a monocyclic unsaturated or saturated or aromatic 10 system containing one or more carbon, nitrogen, oxygen or sulfur atoms or a combination thereof and having 5 or 6 members, e.g. pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiomorpholinyl, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, 1,3-dioxolanyl and 1,4-dioxolanyl.

15 Certain of the above defined terms may occur more than once in the above formula (Ia), and upon such occurrence each term shall be defined independently of the other.

Pharmaceutically acceptable salts forming part of this invention include salts of the carboxylic acid moiety such as alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline and the like, ammonium or substituted ammonium salts, aluminum salts. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprising other solvents of crystallization such as alcohols.

30 The pharmaceutically acceptable salts are prepared by reacting the compound of formula (Ia) with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guandine

and their derivatives etc. may also be used. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

5 The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula (Ia) may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula (Ia) may be prepared by hydrolysing the pure diastereomeric amide.

10

15

20

25

30

35

40

45

50

55

60

65

70

75

80

85

90

95

100

105

110

115

120

125

130

135

140

145

150

155

160

165

170

175

180

185

190

195

200

205

210

215

220

225

230

235

240

245

250

255

260

265

270

275

280

285

290

295

300

305

310

315

320

325

330

335

340

345

350

355

360

365

370

375

380

385

390

395

400

405

410

415

420

425

430

435

440

445

450

455

460

465

470

475

480

485

490

495

500

505

510

515

520

525

530

535

540

545

550

555

560

565

570

575

580

585

590

595

600

605

610

615

620

625

630

635

640

645

650

655

660

665

670

675

680

685

690

695

700

705

710

715

720

725

730

735

740

745

750

755

760

765

770

775

780

785

790

795

800

805

810

815

820

825

830

835

840

845

850

855

860

865

870

875

880

885

890

895

900

905

910

915

920

925

930

935

940

945

950

955

960

965

970

975

980

985

990

995

1000

1005

1010

1015

1020

1025

1030

1035

1040

1045

1050

1055

1060

1065

1070

1075

1080

1085

1090

1095

1100

1105

1110

1115

1120

1125

1130

1135

1140

1145

1150

1155

1160

1165

1170

1175

1180

1185

1190

1195

1200

1205

1210

1215

1220

1225

1230

1235

1240

1245

1250

1255

1260

1265

1270

1275

1280

1285

1290

1295

1300

1305

1310

1315

1320

1325

1330

1335

1340

1345

1350

1355

1360

1365

1370

1375

1380

1385

1390

1395

1400

1405

1410

1415

1420

1425

1430

1435

1440

1445

1450

1455

1460

1465

1470

1475

1480

1485

1490

1495

1500

1505

1510

1515

1520

1525

1530

1535

1540

1545

1550

1555

1560

1565

1570

1575

1580

1585

1590

1595

1600

1605

1610

1615

1620

1625

1630

1635

1640

1645

1650

1655

1660

1665

1670

1675

1680

1685

1690

1695

1700

1705

1710

1715

1720

1725

1730

1735

1740

1745

1750

1755

1760

1765

1770

1775

1780

1785

1790

1795

1800

1805

1810

1815

1820

1825

1830

1835

1840

1845

1850

1855

1860

1865

1870

1875

1880

1885

1890

1895

1900

1905

1910

1915

1920

1925

1930

1935

1940

1945

1950

1955

1960

1965

1970

1975

1980

1985

1990

1995

2000

2005

2010

2015

2020

2025

2030

2035

2040

2045

2050

2055

2060

2065

2070

2075

2080

2085

2090

2095

2100

2105

2110

2115

2120

2125

2130

2135

2140

2145

2150

2155

2160

2165

2170

2175

2180

2185

2190

2195

2200

2205

2210

2215

2220

2225

2230

2235

2240

2245

2250

2255

2260

2265

2270

2275

2280

2285

2290

2295

2300

2305

2310

2315

2320

2325

2330

2335

2340

2345

2350

2355

2360

2365

2370

2375

2380

2385

2390

2395

2400

2405

2410

2415

2420

2425

2430

2435

2440

2445

2450

2455

2460

2465

2470

2475

2480

2485

2490

2495

2500

2505

2510

2515

2520

2525

2530

2535

2540

2545

2550

2555

2560

2565

2570

2575

2580

2585

2590

2595

2600

2605

2610

2615

2620

2625

2630

2635

2640

2645

2650

2655

2660

2665

2670

2675

2680

2685

2690

2695

2700

2705

2710

2715

2720

2725

2730

2735

2740

2745

2750

2755

2760

2765

2770

2775

2780

2785

2790

2795

2800

2805

2810

2815

2820

2825

2830

2835

2840

2845

2850

2855

2860

2865

2870

2875

2880

2885

2890

2895

2900

2905

2910

2915

2920

2925

2930

2935

2940

2945

2950

2955

2960

2965

2970

2975

2980

2985

2990

2995

3000

3005

3010

3015

3020

3025

3030

3035

3040

3045

3050

3055

3060

3065

3070

3075

3080

3085

3090

3095

3100

3105

3110

3115

3120

3125

3130

3135

3140

3145

3150

3155

3160

3165

3170

3175

3180

3185

3190

3195

3200

3205

3210

3215

3220

3225

3230

3235

3240

3245

3250

3255

3260

3265

3270

3275

3280

3285

3290

3295

3300

3305

3310

3315

3320

3325

3330

3335

3340

3345

3350

3355

3360

3365

3370

3375

3380

3385

3390

3395

3400

3405

3410

3415

3420

3425

3430

3435

3440

3445

3450

3455

3460

3465

3470

3475

3480

3485

3490

3495

3500

3505

3510

3515

3520

3525

3530

3535

3540

3545

3550

3555

3560

3565

3570

3575

3580

3585

3590

3595

3600

3605

3610

3615

3620

3625

3630

3635

3640

3645

3650

3655

3660

3665

3670

3675

3680

3685

3690

3695

3700

3705

3710

3715

3720

3725

3730

3735

3740

3745

3750

3755

3760

3765

3770

3775

3780

3785

3790

3795

3800

3805

3810

3815

3820

3825

3830

3835

3840

3845

3850

3855

3860

3865

3870

3875

3880

3885

3890

3895

3900

3905

3910

3915

3920

3925

3930

3935

3940

3945

3950

3955

3960

3965

3970

3975

3980

3985

3990

3995

4000

4005

4010

4015

4020

4025

4030

4035

4040

4045

4050

4055

4060

4065

4070

4075

4080

4085

4090

4095

4100

4105

4110

4115

4120

4125

4130

4135

4140

4145

4150

4155

4160

4165

4170

4175

4180

4185

4190

4195

4200

4205

4210

4215

4220

4225

4230

4235

4240

4245

4250

4255

4260

4265

4270

4275

4280

4285

4290

4295

4300

4305

4310

4315

4320

4325

4330

4335

4340

4345

4350

4355

4360

4365

4370

4375

4380

4385

4390

4395

4400

4405

4410

4415

4420

4425

4430

4435

4440

4445

4450

4455

4460

4465

4470

4475

4480

4485

4490

4495

4500

4505

4510

4515

4520

4525

4530

4535

4540

4545

4550

4555

4560

4565

4570

4575

4580

4585

4590

4595

4600

4605

4610

4615

4620

4625

4630

4635

4640

4645

4650

4655

4660

4665

4670

4675

4680

4685

4690

4695

4700

4705

4710

4715

4720

4725

4730

4735

4740

4745

4750

4755

4760

4765

4770

4775

4780

4785

4790

4795

4800

4805

4810

4815

4820

4825

4830

4835

4840

4845

4850

4855

4860

4865

4870

4875

4880

4885

4890

4895

4900

4905

4910

4915

4920

4925

4930

4935

4940

4945

4950

4955

4960

4965

4970

4975

4980

4985

4990

4995

5000

5005

5010

5015

5020

5025

5030

5035

5040

5045

5050

5055

5060

5065

5070

5075

5080

5085

5090

5095

5100

5105

5110

5115

5120

5125

5130

5135

5140

5145

5150

5155

5160

5165

5170

5175

5180

5185

5190

5195

5200

5205

5210

5215

5220

5225

5230

5235

5240

5245

5250

5255

5260

5265

5270

5275

5280

5285

5290

5295

5300

5305

5310

5315

5320

5325

5330

5335

5340

5345

5350

5355

5360

5365

5370

5375

5380

5385

5390

5395

5400

5405

5410

5415

5420

5425

5430

5435

5440

5445

5450

5455

5460

5465

5470

5475

5480

5485

5490

5495

5500

5505

5510

5515

5520

5525

5530

5535

5540

5545

5550

5555

5560

5565

5570

5575

5580

5585

5590

5595

5600

5605

5610

5615

5620

5625

5630

5635

5640

5645

5650

5655

5660

5665

5670

5675

5680

5685

5690

5695

5700

5705

5710

5715

5720

5725

5730

5735

5740

5745

5750

5755

5760

5765

5770

5775

5780

5785

5790

5795

5800

5805

5810

5815

5820

5825

5830

5835

5840

5845

5850

5855

5860

5865

5870

5875

5880

5885

5890

5895

5900

5905

5910

5915

5920

5925

5930

5935

5940

5945

5950

5955

5960

5965

5970

5975

5980

5985

5990

5995

6000

6005

6010

6015

6020

6025

6030

6035

6040

6045

6050

6055

6060

6065

6070

6075

6080

6085

6090

6095

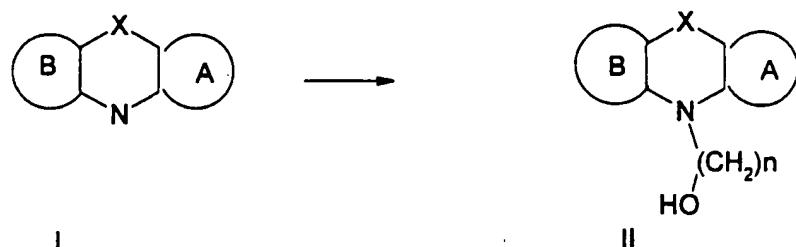
6100

6105

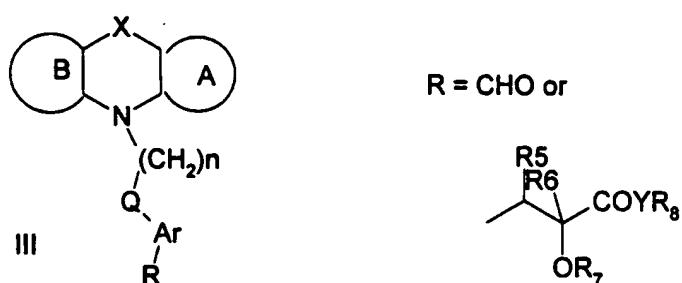
611

A compound of formula (Ia) can be prepared either - when m is equal to 1 - as a compound of formula VI, or b) - when m is equal to 0 - as a compound of formula XII:

5 By alkylating I with a suitable electrophilic reagent to II. (Examples of the electrophilic reagent are: ethylene oxide, ethyl bromoacetate followed by reduction of the ester to alcohol, 2-bromoethanol and 3-bromopropanol)

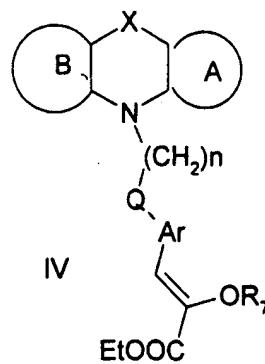


10 The hydroxy group can be converted to a suitable leaving group (for example to a halogen, sulfonate, phosphor under Mitsunobu conditions) and then reacted with HO-Ar-R to give III

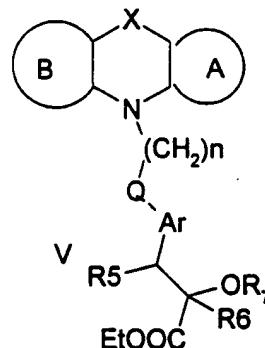


15 When $R = \text{CHO}$, then III can be converted to IV with a Wittig reagent

29

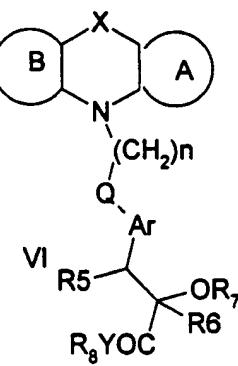


Addition to the double bond of suitable reagents give V



V can either be hydrolysed to the corresponding carboxylic acid or can be reacted further

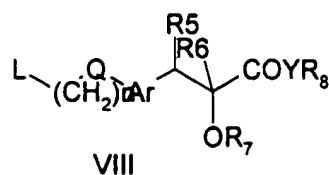
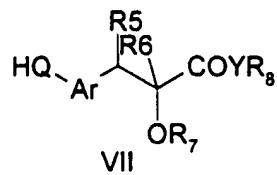
5 with a suitable reagent to give VI



The molecule VII mentioned under formation of II can be synthesised in an analogous way starting from

10 HQ-Ar-CHO.

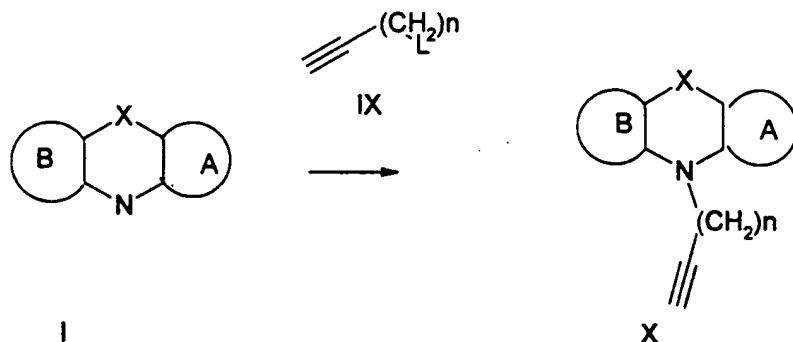
VII can also be reacted with the proper alkylating reagent to give VIII



which then can be reacted with I to give VI.

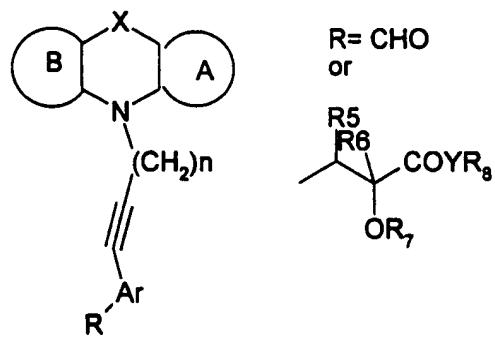
5

Yet another way to synthesise the compounds in this invention is to react I with a proper propargyl analogue IX to give X



X can then be cross coupled with 1-Ar-R using a Pd catalyst like $\text{Pd}(\text{PPh}_3)_4$ or $\text{PdCl}_2(\text{PPh}_3)_2$ to

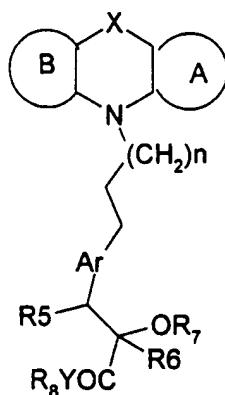
10 give XI



八

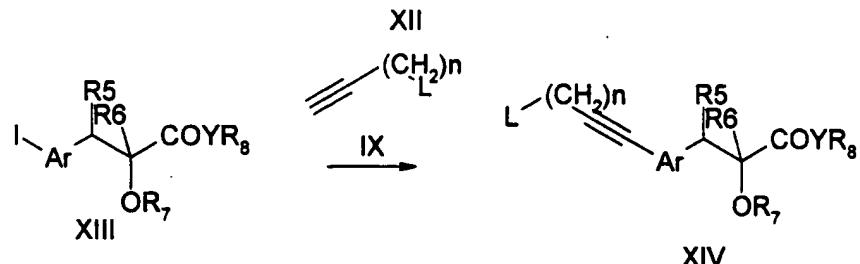
If R= CHO the above synthesis sequence (reaction with a Wittig reagent, hydrogenation followed by hydrolysis or derivatisation of the carboxylic acid) will give the desired product XII

31



XII

The compound XIII can also be cross coupled to the propargyl derivative IX using a Pd catalyst like $\text{Pd}(\text{PPh}_3)_4$ or $\text{PdCl}_2(\text{PPh}_3)_2$ to give the product XIV



5 XIV can then react with I to give XI, which can be reacted further as described above to give XII.

L is a leaving group and all other symbols are as defined earlier.

10

PHARMACOLOGICAL METHODS

In vitro PPAR alpha and PPAR gamma activation activity.

15 Principle

The PPAR gene transcription activation assays were based on transient transfection into human HEK293 cells of two plasmids encoding a chimeric test protein and a reporter protein respectively. The chimeric test protein was a fusion of the DNA binding domain (DBD) from

the yeast GAL4 transcription factor to the ligand binding domain (LBD) of the human PPAR proteins. The PPAR LBD harbored in addition to the ligand binding pocket also the native activation domain (activating function 2 = AF2) allowing the fusion protein to function as a PPAR ligand dependent transcription factor. The GAL4 DBD will force the fusion protein to bind only to Gal4 enhancers (of which none existed in HEK293 cells). The reporter plasmid contained a Gal4 enhancer driving the expression of the firefly luciferase protein. After transfection, HEK293 cells expressed the GAL4-DBD-PPAR-LBD fusion protein. The fusion protein will in turn bind to the Gal4 enhancer controlling the luciferase expression, and do nothing in the absence of ligand. Upon addition to the cells of a PPAR ligand, luciferase protein will be produced in amounts corresponding to the activation of the PPAR protein. The amount of luciferase protein is measured by light emission after addition of the appropriate substrate.

Methods

15

Cell culture and transfection: HEK293 cells were grown in DMEM + 10% FCS, 1% PS. Cells were seeded in 96-well plates the day before transfection to give a confluence of 80 % at transfection. 0.8 µg DNA per well was transfected using FuGene transfection reagent according to the manufacturers instructions (Boehringer-Mannheim). Cells were allowed to express protein for 48 h followed by addition of compound.

Plasmids: Human PPAR α and γ was obtained by PCR amplification using cDNA templates from liver, intestine and adipose tissue respectively. Amplified cDNAs were cloned into pCR2.1 and sequenced. The LBD from each isoform PPAR was generated by PCR (PPAR α : aa 167 - C-term; PPAR γ : aa 165 - C-term) and fused to GAL4-DBD by subcloning fragments in frame into the vector pM1 generating the plasmids pM1 α LBD and pM1 γ LBD. Ensuing fusions were verified by sequencing. The reporter was constructed by inserting an oligonucleotide encoding five repeats of the Gal4 recognition sequence into the pGL2 vector (Promega).

20

Compounds: All compounds were dissolved in DMSO and diluted 1:1000 upon addition to the cells. Cells were treated with compound (1:1000 in 200 µl growth medium including de-lipidated serum) for 24 h followed by luciferase assay.

Luciferase assay: Medium including test compound was aspirated and 100 µl PBS incl. 1mM Mg⁺⁺ and Ca⁺⁺ was added to each well. The luciferase assay was performed using the Luciferase kit according to the manufacturers instructions (Packard Instruments). Light emission was quantified by counting SPC mode on a Packard Instruments top-counter.

5

PHARMACEUTICAL COMPOSITIONS

- 10 In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of the general formula (Ia) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.
- 15 Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.
- 20 Typical compositions include a compound of formula (Ia) or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used.
- 25 For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some
- 30 examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene,
- 35 hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include

any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick,

5 sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring sub-

10 stances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular,

15 intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin

20 capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of formula (Ia) dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The

25 carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, pref-

30 erably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or cap-

sules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

5

Core:

Active compound (as free compound or salt thereof) 5 mg

Colloidal silicon dioxide (Aerosil) 1.5 mg

Cellulose, microcryst. (Avicel) 70 mg

10 Modified cellulose gum (Ac-Di-Sol) 7.5 mg

Magnesium stearate Ad.

Coating:

HPMC approx. 9 mg

15 *Mywacett 9-40 T approx. 0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

20 The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of diseases related to the regulation of blood sugar.

Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

25 The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about

0.1 to about 100 mg, per day may be used. A most preferable dosage is about 0.1 mg to about 70 mg per day. In choosing a regimen for patients it may frequently be necessary to begin with a dosage of from about 2 to about 70 mg per day and when the condition is under

30 control to reduce the dosage as low as from about 0.1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 0.1 to about 100 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

- 5 Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.001 mg to about 100 mg, preferably from about 0.01 mg to about 50 mg of the compounds of formula (Ia) admixed with a pharmaceutically acceptable carrier or diluent.

In a further aspect, the present invention relates to a method of treating and/or preventing type

- 10 I or type II diabetes.

In a still further aspect, the present invention relates to the use of one or more compounds of the general formula (Ia) or pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment and/or prevention of type I or type II diabetes.

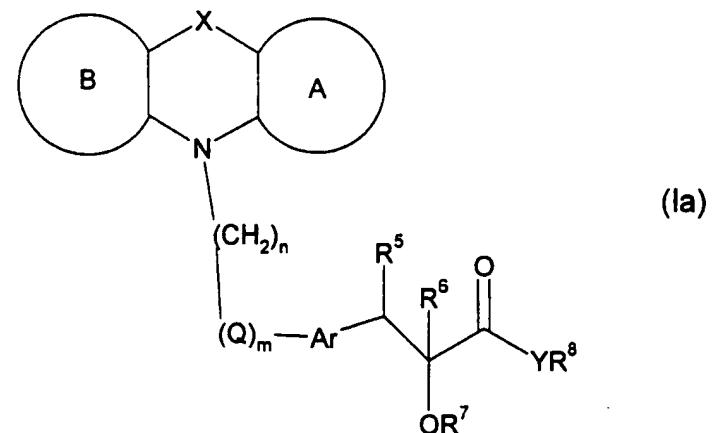
15

Any novel feature or combination of features described herein is considered essential to this invention.

20

Claims:

1. A compound of formula (Ia)



5

wherein ring A fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC₁₋₁₂alkyl, amino, acylamino, C₁₋₁₂alkyl-amino, arylamino, aralkylamino, aminoC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C₁₋₁₂alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₁₂alkyl, aralkoxyC₁₋₁₂alkyl, C₁₋₁₂alkylthio, thioC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆alkoxy or amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

ring B fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, acyl, acyloxy, hydroxyC₁₋₁₂alkyl, amino, acylamino, C₁₋₁₂alkyl-amino, arylamino, aralkylamino, aminoC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl,

aralkoxycarbonyl, $C_{1-12}\text{alkoxy}C_{1-12}\text{alkyl}$, aryloxy $C_{1-12}\text{alkyl}$, aralkoxy $C_{1-12}\text{alkyl}$, $C_{1-12}\text{alkylthio}$, thio $C_{1-12}\text{alkyl}$, $C_{1-12}\text{alkoxycarbonylamino}$, aryloxycarbonylamino, aralkoxycarbonylamino, $-\text{COR}^{11}$, or $-\text{SO}_2\text{R}^{12}$, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, halogen, perhalomethyl, $C_{1-6}\text{alkoxy}$ or amino

5 optionally substituted with one or more $C_{1-6}\text{alkyl}$, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

X is a valence bond, $-(\text{CHR}^9)-$, $-(\text{CHR}^9)-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{O}-$, $-\text{O}-(\text{CHR}^9)-$, $-\text{S}-(\text{CHR}^9)-$, $-(\text{NR}^9)-\text{CH}_2-$, $-(\text{CHR}^9)-\text{CH}=\text{CH}-$, $-(\text{CHR}^9)-\text{CH}_2-\text{CH}_2-$, $-(\text{C=O})-$, $-\text{O}-\text{CH}_2-\text{O}-$, $-(\text{NR}^9)-$, $-(\text{NR}^9)-\text{S}(\text{O}_2)-$, $-\text{CH}=(\text{CR}^9)-$, $-(\text{CO})-(\text{CHR}^9)-$, $-\text{CH}_2-(\text{SO})-$, $-\text{S}-$, $-(\text{SO})-$, $-(\text{SO}_2)-$, $-\text{CH}_2-$, $(\text{SO}_2)-$, $-\text{CH}_2-\text{O}-\text{CH}_2-$, wherein R^9 is hydrogen, halogen, hydroxy, nitro, cyano, formyl, $C_{1-12}\text{alkyl}$, $C_{1-12}\text{alkoxy}$, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, $C_{1-12}\text{alkyl-amino}$, arylamino, aralkylamino, amino $C_{1-12}\text{alkyl}$, $C_{1-12}\text{alkoxycarbonyl}$, aryloxycarbonyl, aralkoxycarbonyl, $C_{1-12}\text{alkoxy}C_{1-12}\text{alkyl}$, aryloxy $C_{1-12}\text{alkyl}$, aralkoxy $C_{1-12}\text{alkyl}$, $C_{1-12}\text{alkylthio}$, thio $C_{1-12}\text{alkyl}$, $C_{1-12}\text{alkoxycarbonylamino}$, aryloxycarbonylamino, aralkoxycarbonylamino, $-\text{COR}^{11}$, or $-\text{SO}_2\text{R}^{12}$, wherein R^{11} and R^{12} independently of each other are selected from hydroxy, halogen, $C_{1-6}\text{alkoxy}$, amino optionally substituted with one or more $C_{1-6}\text{alkyl}$, perhalomethyl or aryl;

10 20 Q is $-\text{O}-$, $-\text{S}-$, $>\text{SO}_2-$, $>\text{NR}^{13}$, wherein R^{13} is hydrogen or $C_{1-6}\text{alkyl}$, Ar represents arylene, heteroarylene, or a divalent heterocyclic group optionally substituted with one or more $C_{1-6}\text{alkyl}$ or aryl; R^4 represents hydrogen, hydroxy, halogen, $C_{1-12}\text{alkoxy}$, $C_{1-12}\text{alkyl}$, $C_{4-12}\text{-alkenynyl}$, $C_{2-12}\text{-alkenyl}$, $C_{2-12}\text{-alkynyl}$ or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R^5 forms a bond together with R^6 , R^6 represents hydrogen, hydroxy, halogen, $C_{1-12}\text{alkoxy}$, $C_{1-12}\text{alkyl}$, $C_{4-12}\text{-alkenynyl}$, $C_{2-12}\text{-alkenyl}$, $C_{2-12}\text{-alkynyl}$, acyl or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R^6 forms a bond together with R^5 , R^7 represents hydrogen, $C_{1-12}\text{alkyl}$, $C_{4-12}\text{-alkenynyl}$, $C_{2-12}\text{-alkenyl}$, $C_{2-12}\text{-alkynyl}$, aryl, aralkyl, $C_{1-12}\text{alkoxy}C_{1-12}\text{alkyl}$, $C_{1-12}\text{alkoxycarbonyl}$, aryloxycarbonyl, $C_{1-12}\text{alkylaminocarbonyl}$, arylamino-carbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

15 25 30

R⁸ represents hydrogen, C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, aralkyl, heterocycl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

Y represents oxygen, sulphur or NR¹⁰, where R¹⁰ represents hydrogen, C₁₋₁₂alkyl, aryl, hy-

5 droxyC₁₋₁₂alkyl or aralkyl groups or when Y is NR¹⁰, R⁸ and R¹⁰ may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C₁₋₆alkyl; n is an integer ranging from 1 to 4 and m is an integer ranging from 0 to 1, provided that A or B does not represent phenyl; or a pharmaceutically acceptable salt thereof.

10

2. A compound according to claim 1 wherein ring A fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl,

15 heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC₁₋₇alkyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl, C₁₋₇alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, 20 perhalomethyl or amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy or cyano.

25 3. A compound according to anyone of the preceding claims wherein ring A fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl; 30 optionally substituted with one or more halogen or hydroxy;

4. A compound according to anyone of the preceding claims wherein ring A fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally

substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy or C₁₋₇alkyl, C₂₋₇alkenyl, C₂₋₇alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heteroaryloxy, heteroaralkoxy, acyl, arylamino, aryloxyC₁₋₇alkyl.

- 5 5. A compound according to anyone of the preceding claims wherein ring A fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy or C₁₋₇alkyl, C₂₋₇alkenyl, C₂₋₇alkynyl, C₁₋₇alkoxy or aryl.
- 10 6. A compound according to anyone of the preceding claims wherein ring A fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen or halogen.
- 15 7. A compound according to anyone of the preceding claims wherein ring B fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇alkenynyl, C₂₋₇alkenyl, C₂₋₇alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC₁₋₇alkyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, 20 aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl, C₁₋₇alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, perhalomethyl or amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; optionally substituted with one or 25 more halogen, perhalomethyl, hydroxy or cyano.
- 25 8. A compound according to anyone of the preceding claims wherein ring B fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇alkenynyl, C₂₋₇alkenyl, C₂₋₇alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl; optionally substituted with one or more halogen or hydroxy.

9. A compound according to anyone of the preceding claims wherein ring B fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy or C₁₋₇alkyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heteroaryloxy, heteroaralkoxy, acyl, arylamino, aryloxyC₁₋₇alkyl.

10. A compound according to anyone of the preceding claims wherein ring B fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen, halogen, perhalomethyl, hydroxy or C₁₋₇alkyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy or aryl.

11. A compound according to anyone of the preceding claims wherein ring B fused to the ring containing X and N represents a 5-6 membered cyclic ring, optionally substituted with one or more hydrogen or halogen.

12. A compound according to anyone of the preceding claims wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂- , -CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -(NR⁹)-CH₂- , -(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-CH₂- , -(C=O)-, -O-CH₂-O-, -(NR⁹)-, -(NR⁹)-S(O₂)-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-(SO)-, -S-, -(SO)-, -(SO₂)-, -CH₂-(SO₂)-, -CH₂-O-CH₂- , wherein R⁹ is hydrogen, halogen, hydroxy, cyano, C₁₋₇alkyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl.

13. A compound according to anyone of the preceding claims wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂- , -CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -(NR⁹)-CH₂- , -(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-CH₂- , -(C=O)-, -O-CH₂-O-, -(NR⁹)-, -(NR⁹)-S(O₂)-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-(SO)-, -S-, -(SO)-, -(SO₂)-, -CH₂-(SO₂)-, -CH₂-O-CH₂- , wherein R⁹ is hydrogen, halogen, hydroxy, C₁₋₇alkyl, C₁₋₇alkoxy, aryl.

14. A compound according to anyone of the preceding claims wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂- , -CH=CH-, -O-(CHR⁹)-, -S-(CHR⁹)-, -(NR⁹)-CH₂- , -(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-CH₂- , -(C=O)-, -O-CH₂-O-, -(NR⁹)-S(O₂)-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-(SO)-, -(SO)-, -(SO₂)-, -CH₂-(SO₂)-, -CH₂-O-CH₂- ,
5 wherein R⁹ is hydrogen, halogen, hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy.

15. A compound according to anyone of the preceding claims wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂- , -CH=CH-, -O-(CHR⁹)-, -(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-CH₂- , -(C=O)-, -O-CH₂-O-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-(SO)-, -
10 (SO)-, -(SO₂)-, -CH₂-(SO₂)-, -CH₂-O-CH₂- , wherein R⁹ is hydrogen.

16. A compound according to anyone of the preceding claims wherein Q is -O- or -S-.

15 17. A compound according to anyone of the preceding claims wherein Q is -O-.

18. A compound according to anyone of the preceding claims wherein Ar represents arylene, heteroarylene, or a divalent heterocyclic group optionally substituted with one or more C₁₋₄alkyl or aryl;

20 R⁵ represents hydrogen, hydroxy, halogen, C₁₋₄alkoxy, C₁₋₄alkyl, C₄₋₇alkenyl, C₂₋₇alkenyl, C₂₋₇-alkyne; or R⁵ forms a bond together with R⁶,
R⁶ represents hydrogen, hydroxy, halogen, C₁₋₄alkoxy, C₁₋₄alkyl, C₄₋₇alkenynyl, C₂₋₇alkenyl, C₂₋₇-alkynyl; or R⁶ forms a bond together with R⁵,
R⁷ represents hydrogen, C₁₋₄alkyl, C₄₋₇alkenynyl, C₂₋₇alkenyl, C₂₋₇-alkynyl, aryl, aralkyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkoxycarbonyl, aryloxycarbonyl, C₁₋₄alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocycl, heteroaryl or heteroaralkyl groups;

25 R⁸ represents hydrogen, C₁₋₄alkyl, C₄₋₇alkenynyl, C₂₋₇alkenyl, C₂₋₇-alkynyl, aryl, aralkyl, heterocycl, heteroaryl or heteroaralkyl;

Y represents oxygen, sulphur or NR¹⁰, where R¹⁰ represents hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl;

30 n is an integer ranging from 2 to 3 and m is an integer ranging from 0 to 1.

19. A compound according to anyone of the preceding claims wherein Ar represents arylene or heteroarylene,
R⁵ represents hydrogen, hydroxy, halogen; or R⁵ forms a bond together with R⁶,
5 R⁶ represents hydrogen, hydroxy, halogen; or R⁶ forms a bond together with R⁵,
R⁷ represents hydrogen, C₁₋₇alkyl, C₂₋₇alkenyl, C₂₋₇alkynyl, aryl, aralkyl, C₁₋₇alkoxyC₁₋₇alkyl, C₁₋₇alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl groups;
R⁸ represents hydrogen, C₁₋₇alkyl, C₂₋₇alkenyl, C₂₋₇alkynyl,;
10 Y represents oxygen or sulphur;
n is an integer ranging from 2 to 3 and m is 1.

20. A compound according to anyone of the preceding claims wherein Ar represents arylene or heteroarylene;
15 R⁵ represents hydrogen;
R⁶ represents hydrogen;
R⁷ represents hydrogen, C₁₋₇alkyl, C₂₋₇alkenyl, C₂₋₇alkynyl, aryl, aralkyl, C₁₋₇alkoxyC₁₋₇alkyl;
R⁸ represents hydrogen, C₁₋₇alkyl, C₂₋₇alkenyl, C₂₋₇alkynyl,;
Y represents oxygen;
20 n is an integer ranging from 2 to 3 and m is 1.

21. A compound according to anyone of the preceding claims wherein Ar represents arylene
R⁵ represents hydrogen;
R⁶ represents hydrogen;
25 R⁷ represents hydrogen, C₁₋₄alkyl, C₂₋₄-alkenyl, C₂₋₄-alkynyl,
R⁸ represents hydrogen, C₁₋₄alkyl,
Y represents oxygen;
n is an integer ranging from 2 to 3 and m is 1.

30 22. A compound according to anyone of the preceding claims wherein Ar represents phenylene,
R⁵ represents hydrogen;
R⁶ represents hydrogen;
R⁷ represents hydrogen, C₁₋₄alkyl,

R⁸ represents hydrogen

Y represents oxygen;

n is an integer ranging from 2 to 3 and m is 1.

- 5 23. A compound according to anyone of the preceding claims wherein A is 5 membered cyclic ring containing S.
24. A compound according to anyone of the preceding claims wherein B is 5 membered cyclic ring containing S.
- 10 25. A compound according to anyone of the preceding claims wherein X is -CH=(CR⁹)-, wherein R⁹ is H.
26. A compound according to anyone of the preceding claims wherein n is 2.
- 15 27. A compound according to anyone of the preceding claims wherein Q is -O-.
28. A compound according to anyone of the preceding claims wherein m is 1.
- 20 29. A compound according to anyone of the preceding claims wherein Ar is phenylene. In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁵ is H.
30. A compound according to anyone of the preceding claims wherein R⁶ is H.
- 25 31. A compound according to anyone of the preceding claims wherein R⁷ is ethyl.
32. A compound according to anyone of the preceding claims wherein Y is oxygen.
- 30 33. A compound according to anyone of the preceding claims wherein R⁸ is H.
34. The compound according to claim 1 which is:
3-[4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-ethoxy]-phenyl]-2-ethoxy-propionic acid,

3-{4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-ethoxy]-phenyl}-2-methoxy-propionic acid,

3-{4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-ethoxy]-phenyl}-2-propoxy-propionic acid,

5 3-{4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-ethoxy]-phenyl}-2-benzyloxy-propionic acid,

3-{4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-ethyl]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-ethyl]-phenyl}-2-methoxy-propionic acid,

10 3-{4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-ethyl]-phenyl}-2-propoxy-propionic acid,

3-{4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-ethyl]-phenyl}-2-benzyloxy-propionic acid,

15 3-{4-[1-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-methoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[1-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-methoxy]-phenyl}-2-methoxy-propionic acid,

3-{4-[1-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-methoxy]-phenyl}-2-

20 benzyloxy-propionic acid,

3-{4-[3-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-propoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[3-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-propoxy]-phenyl}-2-methoxy-propionic acid,

25 3-{4-[3-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-propoxy]-phenyl}-2-benzyloxy-propionic acid,

3-{4-[3-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-propyl]-phenyl}-2-ethoxy-propionic acid,

3-{4-[3-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-propyl]-phenyl}-2-methoxy-

30 propionic acid,

3-{4-[3-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[*f*]azulen-4-yl)-propyl]-phenyl}-2-benzyloxy-propionic acid,

2-Ethoxy-3-(4-(2-(9*H*-1,8,10-triaza-anthracen-10-yl)-ethoxy)-phenyl)-propionic acid,

2-methoxy-3-(4-(2-(9*H*-1,8,10-triaza-anthracen-10-yl)-ethoxy)-phenyl)-propionic acid,

2-propoxy-3-(4-(2-(9*H*-1,8,10-triaza-anthracen-10-yl)-ethoxy)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(2-(9*H*-1,8,10-triaza-anthracen-10-yl)-ethoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(1-(9*H*-1,8,10-triaza-anthracen-10-yl)-methoxy)-phenyl)-propionic acid,
2-methoxy-3-(4-(1-(9*H*-1,8,10-triaza-anthracen-10-yl)-methoxy)-phenyl)-propionic acid,
5 2-benzyloxy-3-(4-(1-(9*H*-1,8,10-triaza-anthracen-10-yl)-methoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propoxy)-phenyl)-propionic acid,
2-propoxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propoxy)-phenyl)-propionic acid,
2-methoxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propoxy)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propoxy)-phenyl)-propionic acid,
10 2-ethoxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propyl)-phenyl)-propionic acid,
2-propoxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propyl)-phenyl)-propionic acid,
2-methoxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propyl)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(3-(9*H*-1,8,10-triaza-anthracen-10-yl)-propyl)-phenyl)-propionic acid,
2-ethoxy-3-(4-(2-(4,5,9-triaza-fluoren-9-yl)-ethoxy)-phenyl)-propionic acid,
15 2-methoxy-3-(4-(2-(4,5,9-triaza-fluoren-9-yl)-ethoxy)-phenyl)-propionic acid,
2-propoxy-3-(4-(2-(4,5,9-triaza-fluoren-9-yl)-ethoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(1-(4,5,9-triaza-fluoren-9-yl)-methoxy)-phenyl)-propionic acid,
2-methoxy-3-(4-(1-(4,5,9-triaza-fluoren-9-yl)-methoxy)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(1-(4,5,9-triaza-fluoren-9-yl)-methoxy)-phenyl)-propionic acid,
20 2-ethoxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
2-methoxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
2-propoxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
25 2-methoxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
2-propoxy-3-(4-(3-(4,5,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
2-ethoxy-3-(4-(2-(1,8,9-triaza-fluoren-9-yl)-ethoxy)-phenyl)-propionic acid,
2-methoxy-3-(4-(2-(1,8,9-triaza-fluoren-9-yl)-ethoxy)-phenyl)-propionic acid,
30 2-propoxy-3-(4-(2-(1,8,9-triaza-fluoren-9-yl)-ethoxy)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(2-(1,8,9-triaza-fluoren-9-yl)-ethoxy)-phenyl)-propionic acid,
2-methoxy-3-(4-(1-(1,8,9-triaza-fluoren-9-yl)-methoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(1-(1,8,9-triaza-fluoren-9-yl)-methoxy)-phenyl)-propionic acid,
2-propoxy-3-(4-(1-(1,8,9-triaza-fluoren-9-yl)-methoxy)-phenyl)-propionic acid,

2-benzyloxy-3-(4-(1-(1,8,9-triaza-fluoren-9-yl)-methoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
2-methoxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
2-propoxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
5 2-benzyloxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
2-methoxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
2-propoxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(3-(1,8,9-triaza-fluoren-9-yl)-propyl)-phenyl)-propionic acid,
10 3-(4-(2-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-ethoxy-propionic acid,
3-(4-(2-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-methoxy-propionic acid,
3-(4-(2-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-propoxy-propionic acid,
3-(4-(2-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(1-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-methoxy-propionic acid,
15 3-(4-(1-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-ethoxy-propionic acid,
3-(4-(1-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-propoxy-propionic acid,
3-(4-(1-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-ethoxy-propionic acid,
3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-methoxy-propionic acid,
20 3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-propoxy-propionic acid,
3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-ethoxy-propionic acid,
3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-methoxy-propionic acid,
3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-propoxy-propionic acid,
25 3-(4-(3-(dithieno[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(2-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-ethoxy-propionic acid,
3-(4-(2-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-methoxy-propionic acid,
3-(4-(2-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-propoxy-propionic acid,
3-(4-(2-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-ethoxy)-phenyl)-2-benzyloxy-propionic acid,
30 3-(4-(1-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-ethoxy-propionic acid,
3-(4-(1-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-methoxy-propionic acid,
3-(4-(1-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-propoxy-propionic acid,
3-(4-(1-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-methoxy)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-ethoxy-propionic acid,

3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-propoxy-propionic acid,
3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-methoxy-propionic acid,
3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propoxy)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-ethoxy-propionic acid,
5 3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-propoxy-propionic acid,
3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-methoxy-propionic acid,
3-(4-(3-(difurano[2,3-*b*;3',2'-*d*]pyrrol-7-yl)-propyl)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(2-(4*H*-1,7-dithia-8-aza-s-indacen-8-yl)-ethoxy)-phenyl)-2-ethoxy-propionic acid,
3-(4-(2-(4*H*-1,7-dithia-8-aza-s-indacen-8-yl)-ethoxy)-phenyl)-2-methoxy-propionic acid,
10 3-(4-(2-(4*H*-1,7-dithia-8-aza-s-indacen-8-yl)-ethoxy)-phenyl)-2-propoxy-propionic acid,
3-(4-(2-(4*H*-1,7-dithia-8-aza-s-indacen-8-yl)-ethoxy)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(1-(4*H*-1,7-dithia-8-aza-s-indacen-8-yl)-methoxy)-phenyl)-2-ethoxy-propionic acid,
3-(4-(1-(4*H*-1,7-dithia-8-aza-s-indacen-8-yl)-methoxy)-phenyl)-2-methoxy-propionic acid,
15 3-(4-(1-(4*H*-1,7-dithia-8-aza-s-indacen-8-yl)-methoxy)-phenyl)-2-benzyloxy-propionic acid,
3-(4-(3-(4*H*-1,7-dithia-8-aza-s-indacen-8-yl)-propoxy)-phenyl)-2-ethoxy-propionic acid,
3-(4-(3-(4*H*-1,7-dithia-8-aza-s-indacen-8-yl)-propoxy)-phenyl)-2-methoxy-propionic acid,
3-(4-(3-(4*H*-1,7-dithia-8-aza-s-indacen-8-yl)-propoxy)-phenyl)-2-propoxy-propionic acid,
3-(4-(3-(4*H*-1,7-dithia-8-aza-s-indacen-8-yl)-propoxy)-phenyl)-2-benzyloxy-propionic acid,
20 3-(4-(3-(4*H*-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-2-ethoxy-propionic acid,
3-(4-(3-(4*H*-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-2-methoxy-propionic acid,
3-(4-(3-(4*H*-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-2-propoxy-propionic acid,
3-(4-(3-(4*H*-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-2-benzyloxy-propionic acid,
2-ethoxy-3-(4-(2-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-ethoxy)-phenyl)-propionic acid,
25 2-methoxy-3-(4-(2-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-ethoxy)-phenyl)-propionic acid,
2-propoxy-3-(4-(2-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-ethoxy)-phenyl)-propionic acid,
2-propoxy-3-(4-(2-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-ethoxy)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(2-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-ethoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(1-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-methoxy)-phenyl)-propionic acid,
30 2-methoxy-3-(4-(1-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-methoxy)-phenyl)-propionic acid,
2-propoxy-3-(4-(1-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-methoxy)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(1-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-methoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propoxy)-phenyl)-propionic acid,
2-methoxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propoxy)-phenyl)-propionic acid,

2-propoxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propoxy)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propoxy)-phenyl)-propionic acid,
2-ethoxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-propionic acid,
2-methoxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-propionic acid,
5 2-propoxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-propionic acid,
2-benzyloxy-3-(4-(3-(4-oxa-1,7-dithia-8-aza-s-indacen-8-yl)-propyl)-phenyl)-propionic acid;
or a pharmaceutically acceptable salt thereof.

35. The compound according to claim 1 which is:
10 3-[4-[2-(8,9-Dihydro-3,5-dithia-4-aza-cyclopenta[f]azulen-4-yl)-ethoxy]-phenyl]-2-ethoxy-
propionic acid;
or a pharmaceutically acceptable salt thereof.

36. A pharmaceutical composition comprising, as an active ingredient, a compound
15 according to any one of the preceding compound claims or a pharmaceutically acceptable
salt thereof together with a pharmaceutically acceptable carrier or diluent.

37. A composition according to claim 36 in unit dosage form, comprising from about 0.05 to
about 100 mg, preferably from about 0.1 to about 50 mg of the compound according to any-
20 one of the preceding compound claims or a pharmaceutically acceptable salt thereof.

38. A pharmaceutical composition useful in the treatment and/or prevention of conditions
mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors
(PPAR), the composition comprising, as an active ingredient, a compound according to any-
25 one of the preceding compound claims or a pharmaceutically acceptable salt thereof
together with a pharmaceutically acceptable carrier or diluent.

39. A pharmaceutical composition useful in the treatment and/or prevention of diabetes
and/or obesity, the composition comprising, as an active ingredient, a compound according
30 to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof
together with a pharmaceutically acceptable carrier or diluent.

40. A pharmaceutical composition for diabetes and/or obesity, the composition comprising,
as an active ingredient, a compound according to anyone of the preceding compound claims

or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

41. A pharmaceutical composition according to any one of the claims 36-40 for oral, nasal,

5 transdermal, pulmonal, or parenteral administration.

42. A method for the treatment of ailments, the method comprising administering to a subject in need thereof an effective amount of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition

10 according to any one of the preceding composition claims.

43. A method for the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the method comprising administering to a subject in need thereof an effective amount of a compound

15 according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to anyone of the preceding claims 36-41.

44. A method for the treatment and/or prevention of diabetes and/or obesity, the method

comprising administering to a subject in need thereof an effective amount of a compound
20 according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to anyone of the preceding claims 36-41.

45. The method according to claims 42-44, wherein the effective amount of the compound according to anyone of the preceding compound claims or a pharmaceutically acceptable

25 salt or ester thereof is in the range of from about 0.05 to about 100 mg per day, preferably from about 0.1 to about 50 mg per day.

46. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament.

30

47. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

48. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment and/or prevention of diabetes and/or obesity.

5

49. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment and/or prevention of diabetes and obesity.

1
INTERNATIONAL SEARCH REPORTInternational application No.
PCT/DK 99/00573

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 487/14, C07D 471/14, C07D 491/153, C07D 495/14, A61K 31/4353,
A61K 31/407, A61P 3/04, A61P 3/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9919313 A1 (DR. REDDY'S RESEARCH FOUNDATION), 22 April 1999 (22.04.99) --	1-49
X	STN International, File CAPLUS, CAPLUS accession no. 1998:430714, DocumentNo. 129:108904, Mitsui Petrochemical Industries, Ltd.: "Preparation of hydroxybenzoic acids, their use as cell adhesion inhibitors, and their pharmaceutical compositions"; JP,A210182550, 19980707 --	1-49
X	WO 9604261 A1 (SMITHKLINE BEECHAM PLC), 15 February 1996 (15.02.96) --	1-49

 Further documents are listed in the continuation of Box C. See patent family annex.

- Special categories of cited documents
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

11 February 2000

Date of mailing of the international search report

22-02-2000

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. + 46 8 666 02 86

Authorized officer

Solveig Gustavsson/EÖ
Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

2

International application No. - - -

PCT/DK 99/00573

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9604260 A1 (SMITHKLINE BEECHAM PLC), 15 February 1996 (15.02.96) --	1-49
X	WO 9725042 A1 (SMITHKLINE BEECHAM P.L.C.), 17 July 1997 (17.07.97) --	1-49
A	WO 9736579 A1 (GLAXO GROUP LIMITED), 9 October 1997 (09.10.97) -- -----	1-49

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/DK 99/00573**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **42-45**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. Claims Nos.: **1-49**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see next sheet

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/0573

Box I.1

Claims 42-45 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

Box I.2

The definition of the rings A and B as a 5-6 membered cyclic ring and Ar as arylene, heteroarylene or a heterocyclic group is too broadly formulated to permit an adequate search. The search has essentially been limited to specific compounds claimed.

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/12/99

International application No.
PCT/DK 99/00573

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9919313 A1	22/04/99	NONE	

WO 9604261 A1	15/02/96	AP 9700918 D AU 697545 B AU 1006199 A AU 3382695 A BG 101180 A BR 9508468 A CA 2196079 A CN 1158123 A CZ 9700254 A EP 0772605 A FI 970357 A GB 9415330 D HU 76637 A IL 114759 D IL 125525 D JP 10503508 T NO 970373 A NZ 292125 A PL 318766 A SK 12297 A TR 960096 A WO 9604260 A GB 9425599 D GB 9509923 D	00/00/00 08/10/98 04/03/99 04/03/96 30/04/98 25/11/97 15/02/96 27/08/97 17/09/97 14/05/97 26/03/97 00/00/00 28/10/97 00/00/00 00/00/00 31/03/98 18/03/97 25/11/98 07/07/97 06/08/97 00/00/00 15/02/96 00/00/00 00/00/00

WO 9604260 A1	15/02/96	AP 9700918 D AU 697545 B AU 1006199 A AU 3382695 A BG 101180 A BR 9508468 A CA 2196079 A CN 1158123 A CZ 9700254 A EP 0772605 A FI 970357 A GB 9415330 D HU 76637 A IL 114759 D IL 125525 D JP 10503508 T NO 970373 A NZ 292125 A PL 318766 A SK 12297 A TR 960096 A WO 9604261 A GB 9425599 D GB 9509923 D GB 2289999 A GB 9501323 D	00/00/00 08/10/98 04/03/99 04/03/96 30/04/98 25/11/97 15/02/96 27/08/97 17/09/97 14/05/97 26/03/97 00/00/00 28/10/97 00/00/00 00/00/00 31/03/98 18/03/97 25/11/98 07/07/97 06/08/97 00/00/00 15/02/96 00/00/00 00/00/00 06/12/95 00/00/00

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/12/99

International application No.
PCT/DK 99/00573

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9725042 A1	17/07/97	AP 9801272 D AU 1439797 A AU 4839196 A BG 102668 A BR 9706968 A CA 2242632 A CN 1212622 A CZ 9802163 A EP 0815091 A EP 0879053 A GB 9600464 D HU 9900560 A IL 125106 D JP 10511977 T NO 974170 A NO 983147 A PL 327731 A SK 92598 A ZA 9700171 A	00/00/00 01/08/97 02/10/96 30/04/99 06/04/99 17/07/97 31/03/99 17/02/99 07/01/98 25/11/98 00/00/00 28/07/99 00/00/00 17/11/98 07/11/97 08/09/98 21/12/98 11/01/99 24/07/98
WO 9736579 A1	09/10/97	AU 2506197 A GB 9606805 D	22/10/97 00/00/00

THIS PAGE BLANK (USPTO)